



**[Billing Code 4140-01-P]**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**National Institutes of Health**

**Government-Owned Inventions; Availability for Licensing**

**AGENCY:** National Institutes of Health, HHS

**ACTION:** Notice

**SUMMARY:** The inventions listed below are owned by an agency of the U.S.

Government and are available for licensing in the U.S. in accordance with 35 U.S.C. 209 and 37 CFR part 404 to achieve expeditious commercialization of results of federally-funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing.

**FOR FURTHER INFORMATION:** Licensing information and copies of the U.S.

patent applications listed below may be obtained by writing to the indicated licensing contact at the Office of Technology Transfer, National Institutes of Health, 6011

Executive Boulevard, Suite 325, Rockville, Maryland 20852-3804; telephone: 301-496-

7057; fax: 301-402-0220. A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

**SUPPLEMENTARY INFORMATION:** Technology descriptions follow.

### **Engineered Antibody Domains with Increased FcRn Binding and *in vivo* Half-life**

**Description of Technology:** Monoclonal antibodies (mAbs) are a fast growing class of new therapeutic molecules. However, their large size remains a significant challenge, preventing them from targeting sterically restricted epitopes and efficiently penetrating into tissues. Smaller antibody fragments and engineered variants are under development to address this challenge, but to date their therapeutic applications have been limited due to rapid clearance and short half-life which greatly decrease their efficacy *in vivo*.

This technology describes two antibody constant domains or binders with increased FcRn binding and *in vivo* half-life. In addition, these binders are small in size (16kDa), very stable, and can be efficiently expressed in *E. coli*. As a result, the binders are particularly well suited as scaffolds for the generation of antibody libraries, from which a desired antigen binders could be developed into therapeutic products with much greater potency compared to existing mAbs. They could also be used as fusion partners to extend the half-life of candidate protein therapeutics.

#### **Potential Commercial Applications:**

- Antibody scaffolds for library construction, and the generation of therapeutics against various diseases.

- Fusion partners to extend the half-life of candidate protein therapeutics.

**Competitive Advantages:**

- Small (16kD) size for better tissue penetration, and in the case of fusion proteins, reduced steric hindrance for therapeutic activity.
- Superior stability compared to isolated CH2 domains and stability comparable to or higher than that of an isolated Fc fragment.
- Exhibit greatly enhanced FcRn binding abilities, including more potent transcytosis and longer *in vivo* half-life.
- Can be efficiently expressed in *E. coli*.

**Development Stage:**

- Early-stage
- In vitro data available
- In vivo data available (animal)

**Inventors:** Dimiter Dimitrov and Tianlei Ying (NCI)

**Intellectual Property:** HHS Reference No. E-136-2014/0 - US Provisional Application No. 62/022,810 filed July 10, 2014

**Licensing Contact:** Whitney Hastings, Ph.D.; 301-451-7337;  
[hastingw@mail.nih.gov](mailto:hastingw@mail.nih.gov)

**Collaborative Research Opportunity:** The National Cancer Institute is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate or commercialize Engineered Antibody Domains. For collaboration opportunities, please contact John D. Hewes, Ph.D. at [john.hewes@nih.gov](mailto:john.hewes@nih.gov) or 240-276-5515.

## **CXCR4 Reduction Leads to Enhancement of Engraftment of Hematopoietic Stem Cells**

**Description of Technology:** Methods of enhancing engraftment of donor hematopoietic stem cells (HSCs) by reducing expression or activity of CXCR4 in HSCs is described. HSC are the only cells in the bone marrow that are both pluripotent and long lived. Bone marrow transplantation (BMT) using HSC is an increasingly common medical therapy for severe hematologic cancers and primary hematologic immunodeficiencies. However, for significant HSC engraftment to occur there must usually be pre-transplant conditioning with either irradiation or chemotherapy or both. The technology described herein shows that it is possible to replace HSC without the need for pre-transplant conditioning regimen. It is known that the chemokine receptor CXCR4 plays a critical role in HSC homing to the bone marrow and in HSC quiescence. The inventors have identified a patient in which one copy of CXCR4 had been deleted in a somatic mutation of an HSC and this cell had clonally repopulated the bone marrow. This led to experiments in mice where the inventors clearly demonstrated in a bone marrow transplantation model, that donor cells with a single copy of the *Cxcr4* gene repopulate recipient mice much faster and last much longer than donor cells having two copies of the *Cxcr4* gene. This technology which shows that HSCs with one copy of the CXCR4 gene have a durable selective advantage in bone marrow repopulation can solve the problem frequently encountered in gene therapy, i.e., the short-lived nature of gene-corrected cells, by utilizing recently discovered gene editing methods that can be used to delete one copy of CXCR4 gene in gene-corrected cells.

**Potential Commercial Applications:**

- Improvement of engraftment in gene therapy protocols and in HSC transplantation.
- Improved bone marrow transplantation, enhancing the efficiency and durability of donor cell repopulation.

**Competitive Advantages:**

- This technology potentially facilitates HSC transplantation without the need of radiation or chemotherapy conditioning.
- This technology may uniquely overcome a major hurdle limiting all gene therapy applications, namely the failure to correct the gene defect over a long time.

**Development Stage:**

- Early-stage
- In vitro data available
- In vivo data available (animal)

**Inventors:** Jiliang Gao, Philip M. Murphy, David H. McDermott, Marie Siwicki, Harry L. Malech, and Joy Liu (all of NIAID)

**Publication:** McDermott DH, et al. Chromothriptic cure of WHIM syndrome. Cell. 2015 Feb 12;160(4):686-99. [PMID 25662009]

**Intellectual Property:** HHS Reference No. E-173-2014/0 - US Patent Application No. 62/026,138 filed July 18, 2014

**Licensing Contact:** Sury Vepa, Ph.D., J.D.; 301-435-5020; [vepas@mail.nih.gov](mailto:vepas@mail.nih.gov)

## **Development of GPR124 Wildtype and Knockout Brain Endothelial Reporter Cells**

**Description of Technology:** There is currently no effective way to block beta-catenin signaling specifically in brain endothelial cells. There is neither an effective way to block beta-catenin signaling stimulated by a particular Wnt family member such as WNT7. The reporter cells created by the NIH investigator from GPR124 knockout mice provide a unique and effective tool to screen for drugs that can specifically interfere with the Wnt7/GPR124 signaling pathway. Such drugs have potential for widespread therapeutic application in the treatment of cerebrovascular diseases, the third leading cause of death in the United States, and a variety of neurodegenerative disorders such as Alzheimer's disease, Parkinson disease, amyotrophic lateral sclerosis, multiple sclerosis, and others.

**Potential Commercial Applications:** Research tools for drug screening.

**Competitive Advantages:** The reporter cells are ideal for screening for drugs that specifically interfere with the Wnt7/GPR124 signaling pathway as the cells have no inherent low level Gpr124 expression.

**Development Stage:** Prototype

**Inventor:** Brad St. Croix (NCI)

**Publication:** Posokhova E, et al. GPR124 functions as a WNT7-specific coactivator of canonical beta-catenin signaling. Cell Rep. 2015 Jan 13;10 (2):123-30. [PMID 25558062]

**Intellectual Property:** HHS Reference No. E-079-2015/0 - Research Tool.  
Patent protection is not being pursued for this technology.

**Licensing Contact:** Betty B. Tong, Ph.D.; 301-594-6565; [tongb@mail.nih.gov](mailto:tongb@mail.nih.gov)

**Collaborative Research Opportunity:** The National Cancer Institute is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize agents that antagonize or promote Gpr124 function. For collaboration opportunities, please contact John D. Hewes, Ph.D. at [hewesj@mail.nih.gov](mailto:hewesj@mail.nih.gov).

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Richard U. Rodriguez, M.B.A.  
Acting Director  
Office of Technology Transfer  
National Institutes of Health

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